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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAO, MANJUNATH N	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/492,029	ZUKER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3-15-04 has been entered.

Claims 1-29 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 3-15-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that modulates the taste signaling in taste cells comprising the use of G-protein beta polypeptides having amino acid sequence SEQ ID NO:3 or 5, does not reasonably provide enablement for such a method comprising the use of G-protein beta polypeptides having amino acid sequence that have sequence identity of greater than 70% when compared to SEQ ID NO:3 or 5. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-29 are so broad as to encompass a method of identifying a compound which modulates the activity of any G-protein beta having 70% identity to an SEQ ID NO: 3 or 5. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the method comprising the sue of only SEQ ID NO:3 or 5. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides in the claimed method. The specification is limited to teaching the use of SEQ ID NO: 3 and 5 as a the G-protein beta but provides no guidance with regard to the making of variants and mutants or with regard to other

uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses a method of using polypeptides with all modifications and fragments of any polypeptide with 70% identity to SEQ ID NOS:3 or 5 because the specification does not establish: (A) regions of the protein structure which may be modified without affecting its activity; (B) the general tolerance of G-protein beta to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue on SEQ ID NO:3 or 5 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides resulting from enormous number of amino acid modifications to SEQ ID NOS: 3 or 5. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics for use in the method is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolskee et al. (WO 93/21337, 10-28-1993), Bruch et al. (JBC, 1987, Vol. 262(5):2401-2404), Levine et al. (Proc. Natl. Acad. Sci. USA, 1990, Vol. 87:2329-2333) or Ray et al. (Gene, 1994, Vol. 149:337-340) and Negulescu et al. (WO 97/48820, 12-24-1997). Claims 1-29 in this instant application are basically drawn to a method of identifying a compound that modulates sensory signaling in taste cells comprising contacting a compound with a taste cell specific G-protein β polypeptide which has greater than 70% amino acid sequence identity to or has the amino acid

sequence with SEQ ID NO:3 or 5 and determining the functional effect of the compound upon the polypeptide wherein the functional effect is determined by either measuring change in intracellular concentration of specific cyclic nucleotides or Ca2+ and wherein the polypeptide is expressed in a cell or a cell membrane. The claims are also directed to methods wherein the functional effect is determined by changes in electrical activity measured by voltage clamp assay or a patch clamp assay etc. and wherein the functional effect is determined by measuring changes in transcription levels of taste cell specific genes and wherein the polypeptides are recombinant or covalently linked to a solid phase support and wherein the polypeptide is from mouse, rat or human or has an amino acid sequence of SEQ ID NO:3 or 5. Claims are also drawn to a method of identifying a compound that modulates the taste signaling comprising expressing the taste cell specific G-protein ß polypeptide, expressing a promiscuous G-protein α polypeptide as well, wherein the promiscuous G-protein α polypeptide is Gα14 or G α15.

Margolskee et al. teach in detail regarding the mechanisms involved vertebrate taste transduction. The reference also teaches that guanine nucleotide binding proteins (G proteins) are heterotrimeric proteins (each having an α , β, and γ sub unit) which mediate signal transduction in olfactory, visual, hormonal and neurotransmitter systems. The reference teaches G proteins are specifically involved in taste transduction. The reference teaches that G proteins couple cell surface receptors to cellular effector enzymes (i.e., phosphodiesterases and adenylate cyclases) and thereby transduce extracellular signals into intracellular second messenger (e.g., cAMP, cGMP, IP3 etc.). The reference also teaches that while α subunit of G protein confers most of the specificity of interaction between its receptor and its effectors in signal transduction process, β and γ subunits appears to be shared among different G proteins. Thus it appears that it

was well known in the art that cyclic nucleotides such as cAMP, cGMP along with G proteins are very much involved in the transduction of taste. The above reference also reveals the involvement of Ca2+ in transduction of taste and involvement of G-proteins. The reference also suggests that compounds with taste lead to taste cell depolarization *via* a G protein mediated rise in cAMP. For example, bitter compounds lead to Ca2+ release from internal stores which is a result of G- protein mediated generation of IP3.

The reference also teaches that over the past decade, efforts have been directed to the development of various agents that interact with taste receptors or mimic or block natural taste stimulants. However, some such taste mimetics have been known not to be suitable for humans either because of high calories they carry or because they are potent carcinogens. Therefore development of new agents that mimic taste or block taste have been limited due to the lack of knowledge of the taste cell proteins responsible for transducing taste modalities and thus there continues to exist a need in the art for new products and methods that are involved in or affect taste transduction. Furthermore, the above reference provides the DNA encoding α subunit called as gustducin of the G-protein involved in taste transduction. The reference also provides methods to identify taste modifying agents which involves identifying agents capable of modulating (mimicking or inhibiting) the interaction of gustducin. Out of the several methods Margolskee et al. propose, one of the method taught is the method of identifying a compound which modulates the activity of the α subunit of the sensory cell associated G-protein by contacting the compound with the α polypeptide only or with α , β and γ polypeptides associated in biologically active form and a radioactively labeled GTP followed by the determination of the rate of conversion of GTP to GDP, which is very similar to the method proposed in the

instant for the β polypeptide. However, the reference does not teach an assay exclusively for identifying a compound that modulates taste signaling in taste cells comprising contacting a compound with a taste cell specific G-protein ß polypeptide or a polypeptide which has an amino acid sequence with SEQ ID NO:3 or 5 or any polypeptide which is 70% identical to SEQ ID NO:3 or 5. The reference is also silent on certain other types of assays such as the use of patch clamp technique or radio labeled ion flux assay etc. even though such techniques have become routine in the art and are well known for studying signal transduction in various types of cells. Bruch et al. for the first time teach the involvement of the common G-protein beta subunit in the taste plasma membranes that stimulates adenylate cyclase and therefore its involvement in signal transduction in taste cells. The reference teaches that G-protein ß subunit was identified by immunoblotting and stimulated adenylate cyclase and co-migrated with the α subunit of the G-protein. While the reference does not teach the amino acid sequence of the ß subunit, Examiner takes the position that such amino acid sequences are inherent to the polypeptide and therefore the reference ß subunit has an amino acid sequence that is identical to that of either SEQ ID NO:3 or 5 or that its amino acid sequence is greater than 70% identical to that of SEQ ID NO:3 or 5. While the reference does not explicitly teach an assay for identification of compounds that modulate sensory signaling in cells, it does teach an assay for the ß subunit of the G-protein and its involvement in taste signal transduction. (Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the

same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594).

Ray et al. teach the cloning of the β polypeptide of sensory cell G-protein which has 100% identity to SEQ ID NO:3. The reference provides cDNA techniques and methods to make recombinant β polypeptide.

Levine et al. teach the cloning of the β polypeptide of sensory cell G-protein which has 97% identity to SEQ ID NO:5. The reference provides cDNA techniques and methods to make recombinant β polypeptide.

Negulescu et al. teach the use of promiscuous G-proteins and their use in identifying G-protein receptors and ligands and compounds that modulate signal transduction. The reference specifically teaches compositions and methods that employ promiscuous G-proteins such as G α 15, detection of activation of promiscuous G-proteins n a variety of assays, including assays in which activation is indicated by a change in fluorescence emission.

Thus it appears that the involvement of the ß subunit of G-proteins in taste signal transduction was well known in the art that there was a concerted effort in the art for identifying compounds which modulate the activity of such G-protein sub units. It also appears that a method for assaying compounds which modulate sensory cell G-protein was also well known in the art. Based on the above knowledge and with the knowledge that the sensory cell G-protein comprises of α, β, and γ polypeptides, and the specific involvement of ß subunit in taste signal transduction as taught by Bruch et al. it would have been obvious to one of ordinary skill in the art to identify agents that specifically modulate the activity of G-proteins in general and β subunit in particular. As Margolskee et al. teach, one would be motivated to do this in order to

identify agents which mimic or block taste and thus such compounds have commercial importance in food and pharmaceutical industry and also due to the fact that some of the known agents are unsuitable for human consumption. One would have a reasonable expectation of success since Bruch et al. clearly show the involvement of ß subunit in taste signal transduction, Margolskee et al. and Negulescu et al. lay the foundation for such methods and also isolate compounds which modulate one of the other factors of sensory cell G-protein, the α polypeptide. Levine et al. and Ray et al. further provide cDNA clones for the β polypeptide of sensory cell G-protein to be used by one skilled in the art contemplating on recombinant methods of expression of such polypeptides.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office action applicants continue to traverse the above rejection mainly arguing that Margolskee et al. while, disclosing Gustducin, a G-protein α subunit specifically expressed in taste cells, does not disclose the taste cell specific G-protein ß subunits of the present invention or its amino acid sequence.

Applicant further argues that Bruch et al. teaches a common G-protein beta subunit is involved in signal transduction of taste cells and does not disclose the amino acid sequence of G-protein beta subunit and that while Ray et al. and Levine et al. disclose the sequence identity of the claimed ß subunits, those polypeptides were cloned from heart cDNA library and have shown its expression in heart and brain but not in taste cells of the tongue.

Applicants argue that Examiner has not identified the reasons for motivation and they do not agree with his reasoning --i.e., that Margolskee et al. "suggest that compounds that modulate

either alpha, beta or gamma (subunit) have commercial value in food and pharmaceutical industry" and that "there was motivation and also a reasonable expectation of success in the art for identifying compounds that modulate taste signal"-- provided by the Examiner. Applicants argue that at best, such a teaching is a general motivation simply *to try* and the reference does not provide a specific motivation for an artisan to use G-protein beta subunit.

Examiner respectfully disagrees with such an argument. This is because the reference of Margolskee et al. specifically refers to other subunits such as the ß and the γ and their use in identification of compounds that modulate the activity of said polypeptides. Applicants' differentiation of motivation as a "general motivation" and a "specific motivation" is highly misplaced without any proper basis. There is no requirement that the motivation must be specific and non-general etc. Contrary to such an argument Examiner maintains his position that the reference of Margolskee et al. does contribute towards the obviousness and motivation for identification of compounds that modulate the activity of G-proteins alpha, beta and gamma involved in taste signal transduction and the question of "obvious to try" never arises.

Next applicants contend, Examiner's argument, that determination of the amino acid sequence of the polypeptide reported by Bruch et al. is well within the knowledge of those skilled in the art, is flawed and the obviousness standard applied is incorrect. Applicants argue that reference of Bruch et al. does not exclude the possibility that other G-protein beta subunits are also involved in taste signaling and Examiner has not established that Bruch's G-protein subunit is one and the same as the G-protein beta subunit of the present invention and the argument of inherency has no basis. Examiner respectfully disagrees with such an argument and counters that applicant's position indeed has no proper basis. This is because applicants'

argument is based on a conjecture and not on solid scientific facts. Applicants provide no scientific reference or scientific basis on which they conclude that there is more than one G-protein beta subunit. Examiner has also not come across any scientific publication reporting the existence of other G-protein beta subunits. Therefore such an argument is not persuasive to overcome the above rejection.

Next applicants argue that the fact pattern in the instant claims is identical to that which existed in the cases of *In re Bell* and *In re Deuel* . Examiner respectfully disagrees with such an argument and reiterates that the fact patterns are not the same and the decisions handed down in the above two cases does not apply here. This is because, in the instant case, applicants are claiming a method of use of a polypeptide and are not claiming a polynucleotide. All arguments applicants have made would have held water if they were claiming a polynucleotide encoding the polypeptide SEQ ID NO:3 or 5. Applicants' argument based on the above two court cases are highly misplaced.

Applicants also argue that as Bruch et al. reference fails to provide the amino acid sequence it is non enabled. Examiner respectfully disagrees with such an argument. As stated above it is well within the knowledge of those skilled in the art to determine the amino acid sequence of a given protein. Furthermore, it would be more so with the published sequences of SEQ ID NO:3 and 5. The requirement of the amino acid sequence is not critical to the above invention. What is critical is the availability of the information that ß-protein is involved in taste signal transduction and that is provided by Bruch et al. reference.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art. Therefore for all the above reasons the rejection is maintained.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Manjunath N. Rao
May 19, 2004